WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

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21 April 1994

Dear Dr Pollard,

... Please find attached a copy of the WHO manual for vaginal colposcopy. It is a more recent version and should replace the one sent to you earlier on.

Yours sincerely,

Dr Marc Karam
Medical Officer
Clinical Research & Product Development
Division of Research and Intervention Development
Global Programme on AIDS

... ENCL.: (1)

)RLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

Rev. 28 Feb. 94

MANUAL FOR THE STANDARDIZATION OF COLPOSCOPY FOR THE EVALUATION OF VAGINALLY ADMINISTERED PRODUCTS

DRAFT

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I. INTRODUCTION

Colposcopy has been primarily developed to detect and define cancerous and precancerous lesions of the cervix. Although it allows inspection of the whole vaginal surface, the ectocervix, transformation zone and lower endocervix are usually the areas of interest to colposcopists. There is an increasing interest in colposcopy as several agencies, research institutions and pharmaceutical companies are currently exploring a range of approaches to develop a vaginal product for the prevention of transmission of HIV and other sexually transmissible agents, for contraception or for both.

The discovery of an *in vitro* anti-HIV activity of spermicides raised the hope of developing a novel method to prevent HIV heterosexual transmission. However, the initial enthusiasm has been countered by the results of several prospective safety and efficacy studies of spermicides (Niruthisard 1991, Roddy 1993, Goeman 1993). These studies showed that the vaginal use of nonoxynol-9- or menfegol-based spermicides generated lesions when used frequently. The nature of the lesions ranged from redness of the mucosa to epithelial disruption. In an efficacy study (Kreiss, 1992) using vaginal sponges impregnated with one gramme of nonoxynol-9, there was an increased risk of genital ulcers and the rate of HIV seroconversion was 43% in women using the sponge versus 36% in those using a placebo, the difference was not statistically significant.

Large intravaginal rings and related devices have been used by gynaecologists for several hundred years to treat utero-vaginal prolapse. The Population Council, the World Health Organization and a number of pharmaceutical companies have developed small-sized rings for intravaginal release of steroids for contraception or for hormone-replacement therapy. All women treated in this way have had regular conventional vaginal and cervical inspections and Papanicolaou smears without any lesions being recognized until very recently. In a study involving 139 women using a levonorgestrel-releasing vaginal ring, there were 48 cases of upper vaginal lesions of varying size and degrees of redness (Bounds 1993). The lesions were described as generalized or circumscribed areas of erythema or irregular areas of small, raised circular or striated ridges. Microbiological testing was normal except for one case of *Candida albicans*. In most cases, the lesions became white on application of 5% acetic acid. Biopsies showed mucosal congestion with widely dilated vessels, chronic inflammatory changes of varying severity and some intercellular oedema. In many cases, the epithelium was thin or even absent. Other centres studying the same type of intravaginal ring have not been able to

findings have

All these studies highlighted the relevance and the importance of colposcopic examination for the evaluation of vaginal products because it is likely that a damage of the mucosa, such as an epithelial disruption, will favour HIV transmission. It needs to be emphasized that routine gynaecological and colposcopic inspection of the vagina and cervix does not usually include visualization of the vaginal fornices, and therefore special protocols must be developed to permit this.

This Manual and these forms have been developed as a result of a Workshop sponsored by the WHO Global Programme on AIDS, the WHO/UNDP/UNFPA/World Bank Special Programme on Research, Development and Research Training in Human Reproduction and attended by expert colposcopists from Australia, Philippines, Thailand and USA together with representatives from the Contraceptive Research and Development Programme (CONRAD), and the Population Council.

II. FACTORS WHICH MAY AFFECT APPEARANCE OF THE VAGINAL MUCOSA

1. Hormonal

1.1 Ovarian hormone secretion

A morphometric study of human vaginal epithelium during the menstrual cycle has demonstrated that there is proliferation and differentiation of the epithelium during the follicular phase reaching a maximum thickness at ovulation (Sjoberg 1988). During the luteal phase, there is shedding of the superficial layers and a steady state with no proliferation of the basal layers resulting in a significantly thinner epithelium in the late luteal phase. Vaginal epithelium has been found to be approximately 46 cell layers thick on day 12 of the menstrual cycle, reducing to approximately 32 layers by day 19 as a result of desquamation (Burgos 1986). Estrogen appears to cause proliferation of the epithelial cells with differentiation, cornification, intracellular glycogen-deposition, formation of desmosomes and increased capillary numbers, dilatation and pore formation. Progesterone prevents the proliferative and differentiation effects of estrogen, and causes

desquamation of superficial cells by loss of desmosomes.

1.2 Exogenous hormone administration

No systematic investigation has been carried out on the colposcopic changes seen on the human cervical and vaginal mucosa during exposure to different exogenous reproductive hormones. Nevertheless, a considerable body of indirect information exists which has bearing on the subject.

Several reports have described the colposcopic findings of excessive estrogen exposure on the cervix (Burghart 1991). The predominant effect is a marked increase in cervical mucus accompanied within a few days by an increase in the visible area of endocervical columnar epithelium (ectopy), and in cervical vascularization. An increased incidence of ectopy also occurs with exposure to combination oral contraceptives (in 50% of users compared with 30% of controls), and is sometimes known as microglandular hyperplasia (El Tawil 1985). Pre-existing ectopy often becomes coarser in appearance, with rapid reversion and transformation on ceasing therapy. Some increase in the incidence of squamous metaplasia may also occur in oral contraceptive users, although data on the effects of oral contraception on preinvasive and invasive cervical neoplasia are inconclusive (Johanisson 1990). In the absence of estrogen, before menarche or after menopause, the cervical and vaginal epithelia become thinner and "atrophic", the intracervical columnar epithelium recedes out of view of the colposcope and the mucosal secretions diminish.

There are no specific colposcopic data on the hormonal effects on the vaginal mucosa of progesterone and progestogens, except in the study of Bounds et al.. These investigators have completed a colposcopic and biopsy study of erythematous lesions on the vaginal and ectocervical mucosa of women using the 20 µg levonorgestrel-releasing contraceptive vaginal ring. Colposcopy demonstrated localized patches or generalized erythema with aceto-white changes (indicating tissue oedema) and an irregular pattern of small, raised circular or striated ridges on the vaginal mucosa. Histology of the biopsies confirmed the presence of widely dilated vessels and intercellular oedema as well as chronic inflammatory changes and thinned or absent mucosa. Resolution of some lesions

occurred during continued therapy, while others resolved after ring removal.

Data from animal and human biopsy studies support the limited colposcopic findings. Detailed toxicology studies in rhesus monkeys (Macaca mulatta) with low dose progesterone, norethisterone and levonorgestrel-releasing vaginal rings have been published (Wadsworth 79a ; Wadsworth 79b) and vaginal histology demonstrated focal or diffuse atrophy of vaginal mucosal epithelium in the majority of animals. The epithelium was thin, non-keratinizing, stratified and squamous. By contrast, the control animals demonstrated well-developed keratinizing, stratified squamous epithelium. Findings were identical with each progestogen. Control animals were fitted with placebo devices, and no adverse local effects were noted. These findings fit with the observation that progesterone prevents the differentiation effect which estrogen produces on human cervical squamous cells in culture (Gorodeski 1989, Gorodeski 1990). In the presence of an intracervical levonorgestrel-releasing device (10 µg per day), the endocervical columnar epithelium exhibited a reduced epithelial height, and there was mild to moderate leucocyte and plasma cell infiltration (El Mahgoub 1982). In depot medroxyprogesterone acetate users there was a significant decrease in the percentage of mucus-producing cervical epithelial cells compared with controls (Gaton 1982).

There are no data indicating the effect of coincident and prolonged oestrogen and progestogen delivered by any route on the squamous epithelium of the human cervix or vagina.

Estrogens cause proliferation of cervical columnar and squamous and vaginal squamous epithelium, and additionally produce maturation with keratinization of the squamous epithelium. Cervical and vaginal squamous epithelia appear to respond similarly to systemic and locally administered hormonal stimuli. High-dose local progesterone causes thinning of the endocervical epithelium. In the vagina, it also prevents squamous proliferation and maturation, and causes shedding of the superficial cell layers with thinning of the mucosa. In the presence of a high local progestogen to estrogen ratio, it could be anticipated that some atrophic mucosal changes would occur, although not to the same extent as noted with progestogen-only devices.

2. Mechanical

It is now apparent from vaginal colposcopy that the vaginal mucosa can be easily traumatized even by routine speculum examination or vaginal sexual intercourse (Norvell 1984) . Factors involved include the frequency, duration, vigour of penile penetration, the degree of natural lubrication, the use of artificial lubricants, the dimensions of the erect penis and the effect of seminal plasma constituents. Genital manipulation, including digital or mechanical masturbation, may also cause epithelial damage. Exogenous factors such as tampon use and douching, use of spermicide-impregnated contraceptive sponges, their frequency of use, need to be considered with respect to cervical mucus production and epithelial vascularity (Fox 1985).

3. Chemical

In addition to their mechanical effect on the mucosa (Berkeley, 1985), the use of tampons has and douching have an effect on the vaginal and cervical mucosa. A mechanism involving chemical irritation was suggested to explain ulcer formation in tampon users (Barrett, 1977). Similarly, cigarette smoking was shown to lead to a vulnerable cervical epithelium (Rogstad, 1993).

4. Infections

Lower genital tract infections are common, affecting up to 25-30% of asymptomatic women of reproductive age. Some of these infections can be detected on gross visual examination (*Candida albicans* infections), or suspected on the presence of a purulent endocervical discharge *Chlamydia trachomatis* infections), or condyloma acuminata (human papilloma virus infection). Most if not all vaginal infections caused by either viruses, yeasts, bacteria or protozoa are associated with colposcopic changes (see photographs). Ulcerations due to *Calymmatobacterium granulomatosis* (donovanosis) are generally located on the external genitalia but can be seen on the vaginal walls. Chancroid, herpes simplex and syphilis lesions can be found on the vagina and the cervix.

Relatively little is known about the importance of most of the above described factors on the vaginal mucosa, or of the implications of findings of device or drug-related lesions. The recognition of minor lesions associated with spermicides or with vaginal ring use, to date, suggests that they are asymptomatic, transient and have no long-term sequelae. Many lesions are probably associated with or exacerbated by sexual activity, tampon-use, or by the gynaecological examination itself and may rapidly heal in spite of continued drug or device use. However, objective data are lacking and need to be systematically collected. A further critical requirement is for agreement on standardization of the examination technique, descriptions and terminology.

This Manual on Vaginal and Cervical Colposcopy is intended as a guideline to be used in studies of new or existing vaginal microbicides, drug delivery systems and vaginally administered spermicides or hormonal contraceptives. The emphasis,in the manual, is placed upon vaginal rather than cervical colposcopy as there are many standard reference texts published concerning the latter. However, it would be remiss not to include cervical colposcopy in a description of vaginal colposcopy. This Manual is not intended as a training document for colposcopy but rather to focus the colposcopist's attention on the hitherto overlooked vaginal fornices and walls.

III. GUIDELINES FOR STANDARDIZING PRACTICAL COLPOSCOPY

Photographic systems such as cervicography are relatively inexpensive and available but they do not allow satisfactory images: impossibility of focusing the cervix and upper vagina in one image and difficulty to visualise the fornices.

The following guidelines are presented as a practical résumé of colposcopic findings. They are reproducible without the aid of computer-based imaging systems.

Technique[1]

1. The subject should be placed on a couch in either the lithotomy position or with leg stirrups so as to enable the perineum and vulva to be inspected.

2. Using low power (x4-10 magnification) and no filter, examine the external genitalia. Note and photograph[2] any positive findings on the external genitalia including the perineum, peri-anal area and the mucosal lining of the introitus.

3. Using higher power (x16-25 magnification) and green filter, re-examine the external genitalia and note and photograph any positive vascular findings.

4. Gently insert a speculum of appropriate size moistened with warm saline into the vagina, so as to enable the cervix and upper vagina to be seen clearly.

5. Carefully open the speculum blades to prevent trauma and bring the cervix into

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[1] In the case a PAP smear is performed before the colpocopy, it is advised to allow an interval of at least 3 weeks or 2 weeks respectively between the 2 examinations, depending on whether the PAP smear resulted in the bleeding of the cervix or not.

[2] Photographs of lesions should be made at X 10 magnification. Higher magnification is to be used only if details are to be shown.

view.

6. If any abnormal vaginal or cervical discharge is seen, perform a wet mount, obtain vaginal pH, and obtain a sample for microbiology.[3]

7. Initial naked eye observation should be performed noting the general state of the cervix and upper vagina.

   a) Hyperaemia which might indicate a vaginitis

   b) Congenital abnormalities

   c) Purulent exudate which might indicate endocervical infection

   d) Bleeding which might make further examination impossible

   e) Macroscopic condylomata

   f) Cervical ulceration which might suggest HSV infection

   g) Mucus retention cysts

   h) Signs of chronic or acute trauma

   i) Foreign bodies

   j) Atrophic changes

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[3] Microbiology of genital discharge:

a. vaginal sample : direct microscopy on wet mount for evidence of *Candida albicans*, *Trichomonas vaginalis*, and clue cells;
b. cervical sample for culture of *Neisseria gonorrhoeae*, culture of *Chlamydia trachomatis* or direct antigen test or PCR.

k) Hyperkeratosis

8. Using low power (x4-10 magnification) and no filter, examine the cervix with regard to the position of the squamo columnar junction and any surface irregularity in the transformation zone. Locate and describe the transformation zone (completely or incompletely visualized, degree of ectopy, presence or absence of oedema, areas of thickened epithelium, nabothian cysts, endo-cervical gland openings, etc). Photograph any significant findings.

9. In a dabbing fashion, gently use a saline-moistened swab to remove any mucus from the cervix. Avoid twisting the swab or rolling it over the surface of the cervix. Still using low power and no filter, describe the cervix as in #8.

10. Using higher power and green filter, examine the vasculature of the cervix and note any positive findings (dilatation, branching patterns, hairpin patterns, etc).

11. Slowly and gently pull back on the speculum (to approximately 3 to 4 cm), to allow visualization of the vaginal fornices.

12. Using a saline-moistened swab, apply pressure to the same side of the cervix as the fornix to be viewed. This will facilitate inspection of the fornix. Perform a systematic naked eye examination of the anterior, right lateral, left lateral, and posterior fornices, noting any positive findings.

13. Using low power, examine the vaginal fornices and photograph any significant findings.

14. Gently reposition the speculum so that the cervix is again in full view.

15. Apply 3-5% acetic acid by gentle irrigation[4] of the surface of the cervix. Wait 30 seconds and re-examine the cervix as in #8. Note and photograph any changes in

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[4]Irrigation is preferred to the use of impregnated swabs which may be traumatic to a fragile mucosa.

the findings (either positive or negative) from previous examination.

16. Using higher magnification and green filter, re-examine the cervical vasculature as in #10.

17. Gently pull back on speculum just enough to visualize all the vaginal fornices and repeat the examination as in #13 and #14.

18. To examine the middle and lower thirds of the vagina, slowly withdraw the speculum with the blades, slightly open so as to separate the vaginal walls, refocussing the colposcope continuously. Note and photograph any relevant finding.

19. Repeat 18 after application of acetic acid.

20. Reexamine the perineal area, the introitus and urethra using the colposcope at X 10 magnification, after application of acetic acid. Note and photograph any relevant finding.

NOTE:

a) At no time should a dry swab be used during examination of either the cervix or the vagina, as this may traumatize the epithelium of either surface. Use large swabs preferably.
b) Record site and size of condylomata.
c) If an endocervical purulent discharge is present, take the appropriate sample for microbiology before application of acetic acid.

Description of findings

Any suspicious area should be described and the characteristics of the following should be considered:

1. Suspicious area

Area which appears different from its surrounding, e.g. discoloration, mass, etc...

2. Epithelium

The integrity of the epithelium should be examined carefully and any manipulation should be done gently to avoid mechanical trauma. A loss of integrity will appear as complete or partial disruption of the epithelium. The following classification is proposed for descriptions of the epithelium:

a. intact: continuity of surface is maintained; includes thinned epithelium.

b. not intact: break in continuity of surface epithelium

i. partial: disruption of epithelial layer without exposing the stroma
ii. complete: disruption of epithelial layer with exposure of the stroma

3. Blood Vessels

a. intact: integrity of vessel wall is maintained with or without dilatation.
b. not intact: break in continuity of blood vessels

4. Oedema

Diffuse accumulation of fluid in interstitial area manifested as swelling and pallor

5. Demarcation

The suspicious area can be either sharply demarcated or diffuse.

6. Peripheral reaction

The existence of a reaction surrounding the lesion should be noted. It generally appears as an hyperaemic reaction or as an inflammatory reaction.

7. Slough:

Existence of a necrotic component in the base of the lesion in the process of separating from the viable layers.

7. Size, site and number

The size of the lesion should be measured where practical with a scale. The site(s) and the number of lesions should be noted on the diagram of the case record form and will serve to monitor the resolution of lesions at subsequent visits.

Table 1 summarises the characteristics of lesions observed during colposcopy.

IV. REPORTING OF FINDINGS

(see attached sheets of Case Record Forms)

WORLD HEALTH ORGANIZATION GLOBAL PROGRAMME ON AIDS

Centre Number ☐ Subject Number ☐☐☐ - ☐

COLPOSCOPY

EXTERNAL GENITALIA

	SALINE APPLICATION	ACETIC ACID APPLICATION
13. Findings 1 normal **(go to Q.17)** 2 abnormal	☐	☐
	Lesion No. 1 2 3 4 5	Lesion No. 1 2 3 4 5
14. Site of suspicious area 1 vulva 2 perineum 3 perianal area		
15. Characteristics of suspicious area* (a) Epithelium (b) Blood vessels (c) Demarcation (d) Peripheral reaction (e) Slough (f) Size (mm)		
16. Diagnosis*		

CERVIX

17. Findings 1 normal **(go to Q.21)** 2 abnormal	☐	☐
	Lesion No. 1 2 3 4 5	Lesion No. 1 2 3 4 5
18. Site of suspicious area 1 cervix 2 fornix		
19. Characteristics of suspicious area* (a) Epithelium (b) Blood vessels (c) Demarcation (d) Peripheral reaction (e) Slough (f) Size (mm)		
20. Diagnosis*		

VAGINA

21. Findings 1 normal **(go to Q.25)** 2 abnormal	☐	☐
	Lesion No. 1 2 3 4 5	Lesion No. 1 2 3 4 5
22. Site of suspicious area 1 upper vagina 2 middle vagina 3 lower vagina		
23. Characteristics of suspicious area* (a) Epithelium (b) Blood vessels (c) Demarcation (d) Peripheral reaction		

CODING SCHEME FOR FINDINGS ON COLPOSCOPY

CHARACTERISTICS OF SUSPICIOUS AREA

(a) Epithelium	1 intact 2 swelling 3 partially disrupted 4 disrupted
(b) Blood vessels	1 intact 2 disrupted
(c) Demarcation	1 sharp 2 diffuse
(d) Peripheral reaction	1 no 2 yes
(e) Slough	1 no 2 yes
(f) Size (mm)	1 less than 5 2 5-10 3 11-15 4 greater than 15

DIAGNOSIS

1 ulcer
2 abrasion
3 ecchymosis
4 petechial haemorrhage
5 sub epithelial haemorrhage plus swelling
6 erythema
7 oedema

COLPOSCOPIC CHARACTERISTICS OF LESIONS

	ULCER	ABRASION	ECCHYMOSIS	PETECHIAL HEMORRHAGE	SUB EPITHELIAL HEMORRHAGE + SWELLING	ERYTHEMA	EDEMA
	disrupted	partially disrupted	intact	intact	intact + swelling	intact	intact + swelling
	intact or disrupted	intact or disrupted	disrupted	disrupted	disrupted	intact	intact
N	sharp	diffuse	sharp or diffuse	sharp	sharp or diffuse	sharp or diffuse	sharp or diffuse
	+/-	+/-	+/-	+/-	+/-	no	+/-
	yes	no	no	no	no	no	no
	any	any	equal or greater than 0.5 cm	less than 0.5 cm	any	any	any

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WORLD HEALTH ORGANIZATION GLOBAL PROGRAMME ON AIDS

Centre Number ☐ Subject Number ☐☐☐ - ☐

COLPOSCOPY

EXTERNAL GENITALIA

	SALINE APPLICATION	ACETIC ACID APPLICATION
13. Findings 1 normal **(go to Q.17)** 2 abnormal	☐	☐
	Lesion No. 1 2 3 4 5	Lesion No. 1 2 3 4 5
14. Site of suspicious area 1 vulva 2 perineum 3 perianal area		
15. Characteristics of suspicious area* (a) Epithelium (b) Blood vessels (c) Demarcation (d) Peripheral reaction (e) Slough (f) Size (mm)		
16. Diagnosis*		

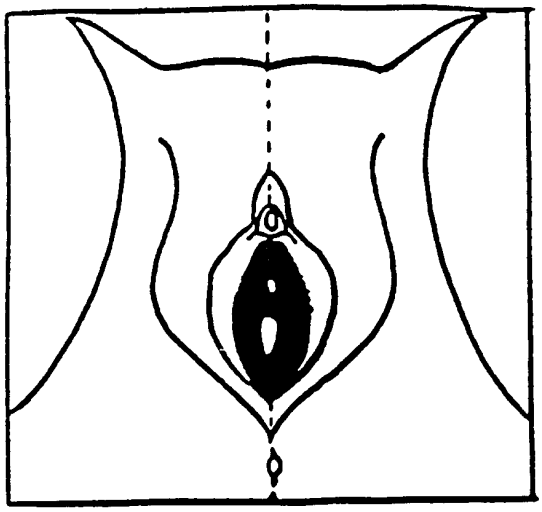
CERVIX

17. Findings 1 normal **(go to Q.21)** 2 abnormal	☐	☐
	Lesion No. 1 2 3 4 5	Lesion No. 1 2 3 4 5
18. Site of suspicious area 1 cervix 2 fornix		
19. Characteristics of suspicious area* (a) Epithelium (b) Blood vessels (c) Demarcation (d) Peripheral reaction (e) Slough (f) Size (mm)		
20. Diagnosis*		

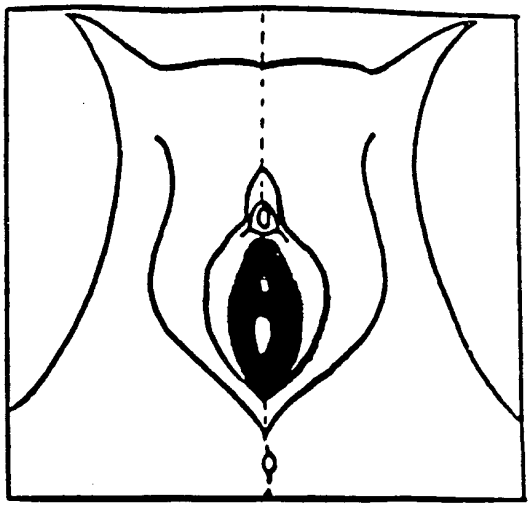
VAGINA

21. Findings 1 normal **(go to Q.25)** 2 abnormal	☐	☐
	Lesion No. 1 2 3 4 5	Lesion No. 1 2 3 4 5
22. Site of suspicious area 1 upper vagina 2 middle vagina 3 lower vagina		
23. Characteristics of suspicious area* (a) Epithelium (b) Blood vessels (c) Demarcation (d) Peripheral reaction		

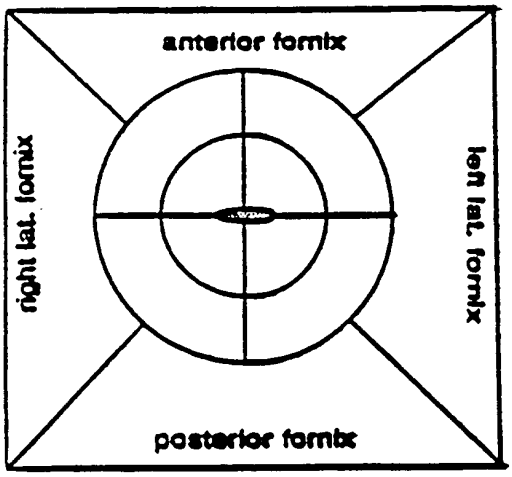
external genitalia



external genitalia



cervix & fornices



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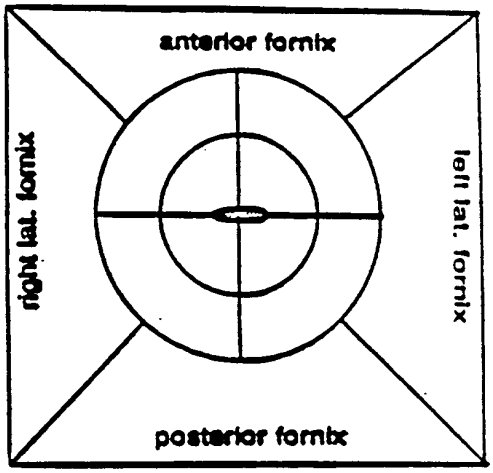
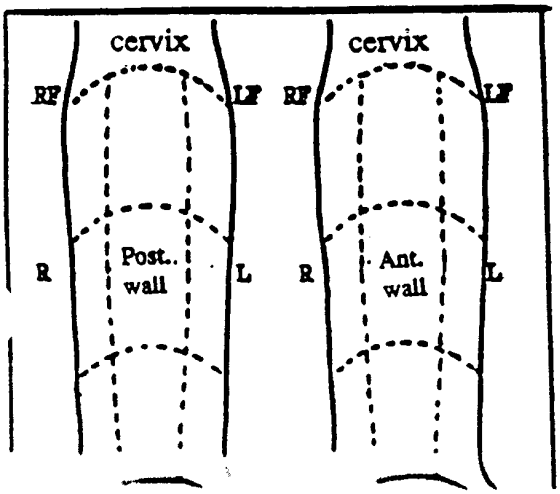
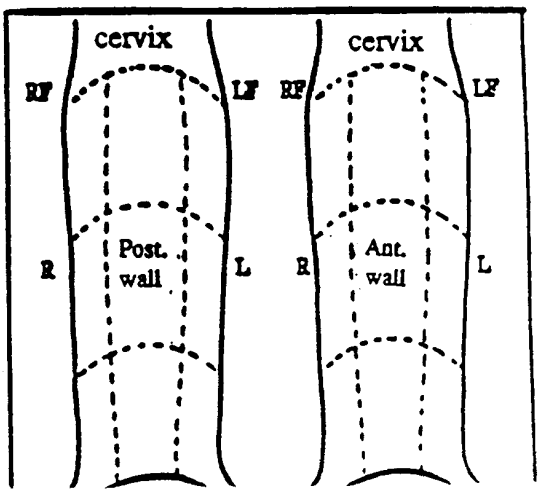


vagina



vagina



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[illegible] of the vagina:

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